3060-1205 & 1813

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Applications of:
PRIEELS, J.P. et al.
08/909879
Serial No. 08/~~442,288~~
Filed: May 16, 1995
For: VACCINE COMPOSITIONS CONTAINING ADJUVANTS

Group Art Unit: 1813
Examiner: L.F. Smith

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APPELLANTS' BRIEF ON APPEAL

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I. INTRODUCTION

In accordance with Rule 192(a), Appellants are filing three copies of this brief and paying a brief filing fee of $300.00. Please charge any additional amount that may be due to Deposit Account No. 06-0916.

II. REAL PARTY IN INTEREST

Application Serial No. 08/442,288 on appeal is assigned to SmithKline Beecham Biologicals S.A.

III. RELATED APPEALS AND INTERFERENCES

This appeal directly affects the appeal in Serial No. 356,372 filed February 17, 1995, which is the parent of the present application. Appellants request that the Board consolidate the appeals in the two applications. Both applications contain the same specification, claims, final rejections, and references. A consolidated appeal would simplify and ease the Board's consideration of the two applications.

Serial No. 08/442,286 filed May 16, 1995 is also a continuation of the present application, but does not relate to this appeal.

IV. STATUS OF CLAIMS

Claims 1-7 and 10-18 presently pend in this application. Appellants are providing a copy of these claims in the attached appendix, as well as in Ex. 2 in the accompanying exhibit book. The Examiner has not allowed any claims in this application.

Along with this brief, Appellants are filing an amendment (Ex. 3) to cancel claim 6 to remove an issue from appeal. Upon entry of the amendment, claims 1-5, 7, and 10-18 will be the only claims pending.

V. STATUS OF AMENDMENTS

Appellants filed an amendment under 37 C.F.R. § 1.116 on November 20, 1996 requesting: (1) cancellation of claims 6 and 13; (2) amendment of claims 1, 3, 12, and 15; and (3) addition of claims 19-29. In the advisory action of December 10, 1996, the Examiner refused entry of this amendment. By an amendment filed with this brief (Ex. 3), Appellants have requested the cancellation of claim 6 to remove an issue from appeal.

VI. SUMMARY OF THE INVENTION

Appellants have discovered a novel and unobvious vaccine composition that enhances the immune response to a given antigen.[1] The inventors surprisingly found that a formulation containing an antigen with a combination of two adjuvants, known as QS21 and 3D-MPL (3-de-O-acylated monophosphoryl lipid A), increases the body's immune response to the antigen. Page 1, line 18 to page 2, line 14.[2] Previous researchers failed to teach or suggest either this particular combination or the resulting enhanced effect on the body's immunity.

QS21 is a purified non-toxic fraction of a saponin[3] from the bark of the South American tree *Quillaja saponaria molina*. Page 1, lines 4-16. U.S. Patent No. 5,057,540 to Kensil (Ex. 7),

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[1] An antigen elicits an adaptive immune response and reacts specifically with corresponding antibodies or T-cell receptors, which are formed in the thymus gland. The antibody or T-cell receptor interacts with the antigen to create an immune response in a mammal. This immunity can then come into play later when the mammal has renewed contact with the antigen. The immune response lies at the heart of many well known vaccines, such as those for chicken pox, measles, polio, and hepatitis. An adjuvant enhances the immune response to the antigen.

[2] All specification cites in this brief are to the parent application Serial No. 356,372 (Ex. 4).

[3] The term "saponin" is broadly used to refer to group of plant glycosides that on shaking with water form colloidal solutions giving soapy lathers.

cited by Appellants at page 1, line 16, of the specification, discloses how to produce QS21 (identified as QA21 in Kensil), as well as other purified saponins from the *Quillaja saponaria molina* tree. Indeed, Kensil notes that 22 different saponins can be purified from this tree's bark. Ex. 7, col. 3, lines 17-46. Of all the different saponins identified and purified from the bark of the *Quillaja saponaria molina* tree, Appellants discovered that it is QS21 that provides the advantageous immune response in combination with 3D-MPL. Page 1, lines 14-16.

3D-MPL is a 3-deacylated monophosphoryl lipid A with 4, 5 or 6 acylated chains. Page 1, lines 9-13. U.S. Patent No. 4,912,094 to Myers (Ex. 12)[4] depicts the formula of 3D-MPL at column 6. Importantly, 3D-MPL differs from MPL (monophosphoryl lipid A) -- 3D-MPL is the de-O-acylated product of MPL. While many monophosphoryl lipids and derivatives are obtained from microorganism, Appellants have discovered that it is 3D-MPL -- in combination with QS21 -- that provides the enhanced immune response.

A vaccine containing an antigen, QS21, and 3D-MPL can be used to treat mammals suffering from or susceptible to a pathogenic infection or cancer. Page 4, line 35 to page 5, line 15. The ratio of QS21 to 3D-MPL typically falls within the range of 1:10 to 10:1, preferably 1:5 to 5:1 and often substantially 1:1. Page 5, lines 30-21. Appellants prefer the range of 2.5:1 to 1:1 of 3D-MPL to QS21. Page 5, lines 31-32.

While the examples in the specification test the antigens rgD_2t and RTS,S, other antigens, such as those disclosed at page 4, line 35 to page 5, line 12, can also be used. Broadly speaking, it is not the identity of the specific antigen that is important to the present invention; rather, it is the combined use of QS21 and 3D-MPL with an antigen to achieve enhanced immune responses.

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[4] The Myers U.S. patent corresponds to UK 2,220,211 cited at page 1, lines 9-13 of Appellants' specification.

VII. ISSUES

This appeal presents three issues to the Board.[5]

1. Are claims 1, 2, 5, 10, 12, 13, and 14 patentable, under 35 U.S.C. § 103, over Long (Ex. 6) in view of Kensil (Ex. 7) and further in view of Schneerson (Ex. 8)?

2. Are claims 1, 3, 4, and 15-18 patentable, under 35 U.S.C. § 103, over Schofield (Ex. 9) or Weiss (Ex. 10) in view of Kensil (Ex. 7) and further in view of Schneerson (Ex. 8)?

3. Are claims 1, 7, and 11 patentable, under 35 U.S.C. § 103, over Cantrell (Ex. 11) in view of Kensil (Ex. 7)?

VIII. GROUPING OF CLAIMS

For purposes of this appeal only, Appellants agree that the patentability of the pending claims, claims 1-5, 7, and 10-18, stands or falls together. Claim 1 reads:

1. A vaccine composition comprising:

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[5] The Examiner has also made a provisional double patenting rejection of the claims of this application over the corresponding claims of related application Serial No. 356,372 ('372 application). Appellants will cancel any conflicting claims in this application upon allowance of claims in the '372 application and, then, if necessary, prosecute any remaining claims or additional claims in the '288 application or a continuation application.

Furthermore, Appellants have filed with this brief an amendment (Ex. 3) canceling claim 6. The cancellation of claim 6 removes from this appeal the only other rejection made by the Examiner in the final office action (Ex. 5), namely a rejection of claim 6 under 35 U.S.C. § 112, ¶ 1. In canceling claim 6, Appellants are not acquiescing that this rejection applies to any other pending claim or that the antigens specified in claim 6 are not within the scope of the pending claims, such as claim 1.

(a) an antigen; and antigenic composition and combinations thereof;

(b) QS21 and

(c) 3-De-O-acylated monophosphoryl lipid A (3D-MPL).

IX. ARGUMENT

The present invention is a unique combination of an antigen and two adjuvants, QS21 and 3D-MPL, which enhances the immune response to the antigen. The prior art, taken as a whole, does not teach this unique combination. Appellants' invention is not obvious.

First, the Examiner failed to establish a prima facie case of obviousness for Appellants' invention. Nothing in the prior art would have led one skilled in the art to select QS21, which comes from a tree, and 3D-MPL, which is obtained from a microorganism, from the numerous other possible adjuvants and use them in combination in a vaccine composition containing an antigen. The Examiner has done nothing more than use Appellants' invention as a roadmap with which to search the prior art to find the individual adjuvants and then argue with hindsight and without any prior art support that it would have been obvious to use this unique combination in a vaccine composition with an antigen. In doing so, the Examiner has erred.

Second, even assuming that the Examiner established a prima facie case of obviousness, the unexpected enhanced results achieved by the claimed vaccine easily overcomes any such prima facie case. The prior art does not teach or recognize that the use of the claimed combination of QS21 with 3D-MPL gives an immune response greater than that achieved individually by QS21 or 3D-MPL. The Examiner has not pointed to a single passage in the prior art that teaches or suggests this enhanced effect.

A. The Examiner Failed to Establish a Prima Facie Case of Obviousness

The Examiner shoulders the burden of establishing a prima facie case of obviousness under 35 U.S.C. § 103. The Examiner can "satisfy this [prima facie] burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references." *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988).

In making this prima facie assessment, it is essential that the PTO forget what it has been taught about the claimed combination by Appellants' specification. *In re Fine*, 837 F.2d at 1075, 5 U.S.P.Q.2d at 1599. "One cannot use a hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *Id.*

Here, the Examiner has relied upon three different combinations of references totaling seven references to reject the pending claims for obviousness. The Examiner's rejection of the claims was improper, as the combined teachings of the prior art do not establish a prima facie case of obviousness. None of the references even hints at the claimed combination let alone suggests the benefits of a vaccine comprising an antigen, QS21, and 3D-MPL.

In the three rejections, the Examiner relied upon Long (Ex. 6), Schofield (Ex. 9), and Weiss (Ex. 10) for disclosure of an antigen in a vaccine composition; Kensil (Ex. 7) to show the use of 3D-MPL; and Schneerson (Ex. 8) or Cantrell (Ex. 11) for a discussion of MPL. While not part of the formal rejections, the Examiner has also cited Myers (Ex. 12) for the alleged interchangeability of MPL and 3D-MPL.

The teachings of these references can be broken down into four categories:

(1) an antigen but neither QS21 nor 3D-MPL--Long (Ex. 6), Schofield (Ex. 9), and Weiss (Ex. 10);

(2) an antigen with QS21 but not 3D-MPL--Kensil (Ex. 7);

(3) an antigen with MPL but neither 3D-MPL nor QS21--Schneerson (Ex. 8) and Cantrell (Ex. 11); and

(4) an antigen with 3D-MPL, not QS21--Myers (Ex. 12).

The prior art must suggest the proposed modification. *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). The invention in *Vaeck* related to the production of the insecticidal *Bacillus* proteins within host cyanobacteria. The Federal Circuit noted that while the references disclosed expression of *Bacillus* genes encoding insecticidal proteins in certain transformed bacterial hosts, nowhere did the cited references disclose or suggest expression of such genes in transformed cyanobacterial hosts, as in the claimed invention. 947 F.2d at 493, 20 U.S.P.Q.2d at 1443. It was not enough for obviousness that bacteria and cyanobacteria were both classified as procaryotes. *Id.*

Similarly, it is not enough that 3D-MPL and QS21 were individually taught as adjuvants for a vaccine composition having an antigen. There must be some teaching or suggestion in the prior art of using these types of adjuvants together, as opposed to the many other possible adjuvants, in such a vaccine composition. That is a fundamental weakness in the Examiner's position that runs as a common thread through each of the three rejections before the Board. Not only does the Examiner lack a specific teaching of suggestion of using 3D-MPL and QS21 together, but the Examiner does not even have a generic teaching pointing to the use of monophosphoryl lipids and saponins together in a vaccine composition.

1. Long with Kensil and Schneerson Fail to Render Prima Facie Obvious Appellants' Claimed Invention

The combined teachings of Long (Ex. 6), Kensil (Ex. 7), and Schneerson (Ex. 8) fail to render prima facie obvious Appellants' invention of using QS21 and 3D-MPL together in a vaccine composition with an antigen. Importantly, this combination of references does not even include 3D-MPL. It is well established that the consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that the claimed invention should be made and would have a reasonable likelihood of success, viewed in the light of the prior art. *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). Clearly, these three references, therefore, could not render prima facie obvious the claimed vaccine composition of an antigen, QS21, and 3D-MPL.

a. Long--Antigen But No QS21 or 3D-MPL

The primary reference--Long (Ex. 6)--lacks any disclosure of either QS21 or 3D-MPL specifically or generically. This reference not only omits any mention of the specific components of interest here, but it is silent about saponins or monophosphoryl lipids generally. Long (Ex. 6), instead, discloses the use of glycoprotein D (gD) subunits to protect against HSV-1 or HSV-2 in mice. In all cases, the gD antigen was formulated in Freund's complete adjuvant. Ex. 6, p. 761. The Examiner admits that "[i]t is very well known that Freund's complete adjuvant is not suitable for human use." Ex. 5, p. 8.

While the Examiner speculates that one skilled in the art would have used other adjuvants if the gD antigen was to be used in humans, Long discloses none. Nor does the Examiner cite a reference to substantiate her assertion. Such speculation does not rise to the level of a prior art teaching. Even the human use of the gD subunit vaccine is speculative given Long's conclusion

that "[i]t remains to be seen whether such a subunit vaccine [gD] will protect against establishment of latency or recurrent infection." Ex. 6, p. 763.

At best, Long (Ex. 6) teaches nothing more than that an adjuvant, particularly Freund's complete adjuvant, can be used with an antigen in a vaccine. Appellants do not contest that antigens and adjuvants were known prior to Appellants' invention. What Appellants invented, however, was the unique combination of two adjuvants--QS21 and 3D-MPL.

The Examiner's reliance on Kensil (Ex. 7) and Schneerson (Ex. 8) to show those two components in combination is misplaced. Obvious to try or obvious to experiment is not enough to establish obviousness. *In re Dow Chemical*, 837 F.2d at 473. Furthermore, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *In re Vaeck*, 947 F.2d at 493, 20 U.S.P.Q.2d at 1442. The Examiner cannot rely upon Appellants' disclosure for this expectation of success. *Id.* With a properly applied obviousness standard, it is clear that nothing would have led to the combined use of these two specific adjuvants with any expectation of success.

b. Kensil--Only QS21

Kensil (Ex. 7) discloses how to purify at least 22 different saponins, including QS21, from the *Quillaja saponarioa Molina* tree. Kensil notes that these purified saponins are useful as immune adjuvants and enhance immune responses at much lower levels than the previously available heterogeneous or crude saponin preparation. Ex. 7, col. 3, lines 40-46. While Kensil notes that purified saponins can be administered together with non-saponin adjuvants, there is no mention of monophosphoryl lipids, much less 3D-MPL. Rather, Kensil lists oil adjuvants,

liposomes, mineral salts, polynucleotides, and certain natural substances. Ex. 7, col. 7, lines 22-31.

If anything, Kensil would have led one skilled in the art to use one of the 22 saponins in combination with other saponins or the specified adjuvants listed at column 7, lines 22-31. Nothing tells one skilled in the art to ignore these adjuvant combinations of Kensil. There is no teaching or suggestion of the specific combination of QS21 and 3D-MPL.

c. Schneerson--Only MPL, Not 3D-MPL

Schneerson (Ex. 8) does not even disclose 3D-MPL. It relates to monophosphoryl lipid A (MPL). As Appellants pointed out during prosecution, 3D-MPL is a de-acylated form of MPL. The Examiner does not dispute this.

Furthermore, the only combination of adjuvants taught by Schneerson is MPL with trehalose dimycolate (TDM), a cell wall extract of a mycobacterium. Ex. 8, p. 2136. There is no mention of QS21 or other saponins. Again, nothing in the prior art would have led the skilled artisan to toss aside these teachings of specific adjuvant combinations and replace them with QS21 and 3D-MPL, especially when neither Long (Ex. 6), Kensil (Ex. 7), nor Schneerson (Ex. 8) has anything to do with 3D-MPL.

d. Myers--Only 3D-MPL

When faced with this glaring error, the Examiner cited Myers (Ex. 12) and argued that the MPL adjuvant disclosed in Schneerson (Ex. 8) appears to be an obvious or analogous variant of the claimed 3D-MPL. Ex. 5, pages 10 and 14. In reaching out to Myers (Ex. 12), the Examiner admits that she needs four references to establish the supposed obviousness of a three component vaccine combination. That alone tells the weakness of the Examiner's position.

Although Myers mentions that 3D-MPL can be used in place of MPL as an adjuvant (Ex. 12, col. 9, line 62 to col. 10, line 3), Myers fails to disclose what other adjuvants, especially saponins such as QS21, should be used in combination with the 3D-MPL. Myers, therefore, does not solve the Examiner's problem of lacking a teaching that would have suggested to one skilled in the art that QS21 and 3D-MPL should be used together as adjuvants in a vaccine composition. Myers does not disclose even the generic combination of a saponin with a monophosphoryl lipid. It merely invites one to try 3D-MPL in unrelated adjuvant combinations with no expectation of success.

The cited prior art would not have led one skilled in the art to use a specific saponin, QS21, with a specific de-acylated monophosphoryl lipid, 3D-MPL, with an antigen in a vaccine composition. Not only does the Examiner lack a teaching suggesting the combination of the two adjuvants QS21 and 3D-MPL, but the Examiner does not even have a teaching of using a saponin (e.g., QS21) with a monophosphoryl lipid (e.g., 3D-MPL) as adjuvants in a vaccine composition. Hence the Examiner's position is fundamentally flawed. Therefore, the Examiner's rejection of Long with Kensil and Schneerson (and even Myers) fails to meet the prima facie threshold. The Board should reverse the Examiner's rejection.

2. Schofield or Weiss with Kensil and Schneerson Fail to Render Prima Facie Obvious Appellants' Invention

The second rejection based on Schofield (Ex. 9), Weiss (Ex. 10), Kensil (Ex. 7), and Schneerson (Ex. 8) likewise falls short of teaching the claimed vaccine. These references, taken as a whole, do not render prima facie obvious the claimed combination of an antigen, QS21, and 3D-MPL in a vaccine composition.

Kensil and Schneerson miss the mark, as discussed above. Kensil tells one to use QS21, but not 3D-MPL. Schneerson relates to MPL, but not 3D-MPL or QS21. Nor is there any generic teaching in Kensil or Schneerson of a saponin with a monophosphoryl lipid, again a fundamental flaw in the Examiner's position.

The primary references, Schofield (Ex. 9) and Weiss (Ex. 10), do not cure these defects because they have nothing to do with QS21 or 3D-MPL or, for that matter, saponins or monophosphoryl lipids. These references surely could not tell the skilled artisan to pick out QS21 and 3D-MPL from the many possible adjuvants and use them together.

Specifically, Schofield (Ex. 9) describes the immunization of rats with irradiated *Plasmodium berhei sporozoites* without any discussion of what, if any, adjuvants to use, much less QS21 or 3D-MPL. Schofield leaves one guessing.

Weiss (Ex. 10) relates to the immunization of mice with live sporozoites and the development of T cell-mediated immunity without any discussion of what, if any, adjuvants are to be used. As with Schofield (Ex. 9), this prior art leaves one groping in the dark. Neither Weiss (Ex. 9) nor Schofield (Ex. 9) even generically discloses the adjuvant class for QS21 or 3D-MPL. Lacking such a fundamental teaching, these references could not have led one to the specific adjuvants of QS21 and 3D-MPL.

Therefore, the cited teachings of Schofield or Weiss with Kensil and Schneerson fail to teach or suggest the claimed vaccine composition. The Examiner's rejection falls far short of the prima facie threshold and should be reversed.

3. Cantrell with Kensil Fail to Render Prima Facie Obvious Appellants' Invention

As with the other rejections, the cited prior art of Cantrell with Kensil merely teaches that QS21 and MPL possibly can be used individually as adjuvants without any teaching that QS21 and 3D-MPL (as opposed to MPL) should be used together in a vaccine composition. Lacking such a critical teaching, the prior art, taken collectively, cannot render prima facie obvious the claimed invention.

Cantrell (Ex. 11) discloses vaccines containing tumor antigens with MPL (but not 3D-MPL) as a immunostimulant. Ex. 11, col. E, lines 33-43. The three classes of adjuvants mentioned by Cantrell, however, are derived from bacteria, i.e., (i) mycobacterial cell wall skeleton, (ii) trehalose dimycolates (TDM), and (iii) pyridine soluble extract of a microorganism. There is no mention of an adjuvant from a tree bark or any other saponin, specifically or generically, for use with the MPL, much less 3D-MPL. Ex. 11, col. 4, line 48 to col. 5, line 43. Thus, Cantrell provides no rationale to combine QS21 (a tree bark derived saponin) with an adjuvant from 3D-MPL, an adjuvant derived from a bacteria.

As in the other rejections, when the failure of Cantrell to disclose 3D-MPL was pointed out to the Examiner, the Examiner relied upon Myers (Ex. 12) to show the alleged interchangeability of MPL and 3D-MPL. But, Myers, as discussed above, does not teach one skilled in the art to use the 3D-MPL in combination with a saponin, such as QS-21.

While Kensil (Ex. 7) discloses how to purify at least 22 different saponins, including QS21, nothing in Kensil would have led one skilled in the art to use QS21 in combination with 3D-MPL. Kensil merely notes that the purified saponins are useful as immune adjuvants and enhance immune responses at much lower levels than the previously available heterogeneous or

crude saponin preparation. Ex. 7, col. 3, lines 40-46. While Kensil states that the purified saponins can be administered together with non-saponin adjuvants such as oil adjuvants, liposomes, mineral salts, polynucleotides, and certain natural substances, there is no mention of 3D-MPL specifically or generically. Ex. 7, col. 7, lines 22-31.

In a case similar to the present one, *In re Geiger*, 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987), the Federal Circuit emphasized that "[o]bviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion, or incentive supporting combination." There, the inventors claimed a method of inhibiting scale formation on and corrosion of metallic parts in cooling water systems by use of compositions containing three components: (1) a copolymer of sulfonated styrene/maleic anhydride, (2) a water soluble zinc compound, and (3) an organo-phosphorus acid compound or water soluble salt. The collective prior art taught using each of these three components, separately or in a combination falling short of that claimed, for treating cooling water systems. Yet, the Federal Circuit held that was not enough for a prima facie case. While acknowledging that combining the three components of the claimed invention may have been obvious to try, the court stated that does not constitute the standard for combining references under § 103. *Id.* at 687; 2 U.S.P.Q.2d at 1277.

Likewise, in *In re Dow Chemical*, 837 F.2d 469, 5 U.S.P.Q.2d 1529, the Federal Circuit reversed a rejection of claims directed to a three component polymer (i.e., styrene, maleic anhydride, and synthetic diene rubbers), over two prior art references. One reference disclosed a polymeric resin composed of diene rubber and styrene, and the second reference taught a technique for preparing maleic anhydride-styrene copolymers. The Federal Circuit held that the rejection presented an obvious to experiment standard for obviousness, which does not meet the

requirements of § 103. *Id.* at 473, 5 U.S.P.Q.2d at 1532. The court stated that the rejection must be reversed because the cited prior art did not suggest that any process could be used successfully in this three-component system to produce the claimed product having the desired properties. *Id.*

The prior art relevant to the present invention, at best, shows that the claimed components were known and used individually in vaccine compositions. Appellants, however, departed from the state of the art and discovered the unique combination of QS21 and 3D-MPL. The claimed vaccine composition is not prima facie obvious.

4. Conclusion--No Prima Facie Obviousness

It is not enough that QS21 and 3D-MPL appear separately in the prior art; the prior art most provide some motivation for putting them together to form the claimed vaccine. The Examiner merely sets forth arguments that it might have been obvious to try to use these two components together with an antigen. But, obvious to try is not sufficient for a prima facie obviousness case. The Examiner, accordingly, has not met the burden for a prima facie case of obviousness.

B. Unexpected Enhanced Immune Effect Rebuts Any Prima Facie Case of Obviousness

Even if the Board holds that the Examiner has established a prima facie case of obviousness, the claimed vaccine composition is still patentable over the prior art. The unexpected enhanced results achieved by the claimed vaccine composition overcomes any such prima facie case. The Examiner has improperly ignored these improved results. *In re Corkill,* 771 F.2d 1496, 1501, 226 U.S.P.Q.2d 1005, 1010 (Fed. Cir. 1985) ("A greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness . . . .")

Appellants' data evidence the improved immune properties flowing from use of the claimed vaccine. The combination of QS21 and 3D-MPL provides an effect that is larger than the sum of the separate effects of each adjuvant. Page 14, lines 18-20. This enhanced effect allows for the use of less antigen to achieve the same immune response as in the absence of the combination of QS21 and 3D-MPL.

Appellants' specification, example 1 at pages 6-9, describes the administration to mice formulations of the antigen rgD_2t for Herpes Simplex Virus (HSV) with either (i) QS21, (ii) 3D-MPL, or (iii) QS21 and 3D-MPL in dosages of antigen ranging from 0.0 to 10.0 μg/ml. Subsequently, the mice's lymph nodes were measured for secretion of interferon (IFN)-γ, which is produced, *inter alia*, from the T lymphocytes and is associated with protective responses. IFN-γ is an important cytokine that regulates T cell responses. Furthermore, IFN-γ itself has cytokinic activities and may further enhance the killing of intracellular pathogens.

As shown by the data in the table at page 9, at antigen levels of 0.1 and 1.0 μg/ml, the IFN-γ secretion for QS21 and 3D-MPL was more than twice the secretion for the individual responses. At 0.1 μg/ml antigen, while QS21 and 3D-MPL individually measured IFN-γ secretions of <50 pg/ml or 143 pg/ml, combined they produced secretion levels of 335 pg/ml. At 1.0 μg/ml antigen, while QS21 and 3D-MPL individually measured IFN-γ secretions of 116 pg/ml or 192 pg/ml, combined they produced secretion levels of 914 pg/ml, three times the sum of the individual responses. Page 8, line 9 to page 9, line 10.[6]

Similarly, the data for example 2 at pages 9 to 12 establish this enhanced effect. Appellants gave mice dosages of the combined hepatitis B and malarial antigen RTS,S, made by

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[6] It is believed that no enhanced effect was seen at 10 μg/ml antigen due to the large amount of antigen used in comparison to the adjuvants.

recombinant technology, with either (i) QS21, (ii) 3D-MPL, or (iii) QS21 and 3D-MPL. Appellants then measured the ability of the formulations to induce cytotoxic T lymphocyte (CTL) cells, which kill target cells and are associated with the immune response. Page 2, lines 5-27. Formulations having both QS21 and 3D-MPL yielded CTL activity (as measured by % specific lysis) significantly greater than the sum of the levels for QS21 or 3D-MPL alone. Table, page 12. Immunization with the RTS,S antigen with just QS21 induced CTL activity at levels 1/30th of that for the combination of QS21 and 3D-MPL, while the RTS,S antigen with just 3D-MPL did not even induce CTL activity. Page 12, lines 1-14.

This finding of CTL activity for the combination of QS21 and 3D-MPL with a recombinantly made antigen, RTS,S, has important implications for the use of recombinant molecules as the antigen. While CTL induction generally occurs when the target antigen is synthesized intracellularly (e.g., in infections by viruses, intracellular bacteria, or in tumors), CTL induction generally does not occur when the antigen is a non-living antigen, such as one made by recombinant technology. Page 2, lines 15-24. Appellants thus discovered that the unique combination of QS21 and 3D-MPl triggers CTL induction even when the antigen is recombinantly made. Appellants believe that the present invention will open the door to the use of more recombinantly made antigens, such as RTS,S, than has been possible.

Turning next to the data in the Rule 132 Declaration of Dr. Garcon (Ex. 13), it likewise compels a finding of patentability. The declaration provides data showing unexpected enhancement of the immune response with various antigens.

First, in figure 1 and paragraph 3, Dr. Garcon demonstrated the enhanced effect of QS21 and 3D-MPL together with a hepatitis B antigen (HBV) compared to QS21 or 3D-MPL alone. For example, 25 μg of 3D-MPL alone gave antibody titers of about 2 million units. 10 μg QS21

alone gave a value barely above zero. Yet, the combination of 25 μg 3D-MPL with 10 μg QS21 yielded a value near 4 million.

Second, in table 1 and paragraph 4, Dr. Garcon established that QS21 and 3D-MPL together provided a significantly more pronounced IgG2a response to the S antigen of hepatitis B than 3D-MPL alone or with alum. 3D-MPL and alum provided a value of 13,823; alum alone gave a value of 122; and the combination of QS21 and 3D-MPL jumped the value to 23,038.

Third, in table 2 and paragraph 5, Dr. Garcon explained how mice were immunized with 20μg of HIV gp 120 formulated with various adjuvant formulations. Dr. Garcon concluded that the combined formulation of the invention significantly enhanced Interferon ϒ responses (27 ng/ml for the combination versus 5 ng/ml for 3D-MPL or 15 ng/ml for QS21) and interleukin IL2 production (0.8 IU/ml for QS21/3D-MPL compared to 0.2 IU/ml for 3D-MPL or 0.4 for QS21).

Fourth, in tables 3 and 4 and paragraph 6, Dr. Garcon showed that the combination of QS21 and 3D-MPL unexpectedly enhanced the antibody titers to a RSV antigen (table 3) and the stimulation index (CMI) following administration of a RSV antigen (table 4).

The Board cannot ignore this enhanced effect of QS21 with 3D-MPL. The claimed combination of two specific adjuvants raises immune responses to levels not seen by either adjuvant alone. Nothing in the prior art taught or suggested the enhanced levels of immune response obtained by the claimed combination of QS21 and 3D-MPL. Appellants are not claiming that they discovered QS21 or 3D-MPL; Appellants did, however, discover the combination of QS21 and 3D-MPL and the significantly enhanced immune response flowing from the use of this duo in a vaccine.

X. CONCLUSION

Appellants have discovered an unique and nonobvious combination of two specific adjuvants--QS21 and 3D-MPL--that significantly enhances the immune response. The prior art neither taught nor suggested this combination that could open up a whole new field of vaccines using recombinantly made antigens. Appellants, accordingly, are entitled to a patent for the subject matter of the appealed claims.

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APPENDIX

CLAIMS--S.N. 08/442,288

1. A vaccine composition comprising:

(a) an antigen; and antigenic compositions and combinations thereof;

(b) QS21 and

(c) 3-De-O-acylated monophosphoryl lipid A (3D-MPL).

2. A vaccine as claimed in claim 1 wherein the ratio of QS21:3D-MPL is from 1:10 to 10:1.

3. A vaccine composition as claimed in claim 1 capable of invoking a cytolytic T cell response in a mammal to the antigen or antigenic composition.

4. A vaccine composition as claimed in claim 1 capable of stimulating interferon γ production.

5. A vaccine composition as claimed in claim 2 wherein the ratio of QS21:3D-MPL is from 1:1 to 1:2.5.

6.[1] A vaccine composition as claimed in claim 1 comprising an antigen or antigenic composition derived from the group consisting of Human Immunodeficiency Virus, Feline Immunodeficiency Virus, Herpes Simplex Virus type 1, Herpes Simplex virus type 2, Human cytomegalovirus, Hepatitis A, B, C or E, Respiratory Syncytial virus, human papilloma virus, Influenza virus, *Salmonella, Neisseria, Borrelia, Chlamydia, Bordetella, Plasmodium* and *Toxoplasma.*

7. A vaccine as claimed in claim 1 wherein the antigen is a tumor antigen.

10. A method of treating a mammal suffering from or susceptible to a pathogenic infection comprising the administration of a safe and effective amount of a composition according to claim 1.

11. A method of treating a mammal suffering from cancer comprising the administration of a safe and effective amount of a composition according to claim 1.

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[1] By an amendment filed with this brief, Appellants have canceled claim 6.

12. A process for making a vaccine composition according to claim 1 comprising admixing QS21 and 3D-MPL with an antigen, antigenic composition or combination thereof.

13. A vaccine composition as claimed in claim 1 comprising an antigen or antigenic composition derived from the group consisting of Herpes Simplex Virus type 1, Herpes Simplex virus type 2, Human cytomegalovirus, Hepatitis A, B, C, or E, Respiratory Syncytial virus, human papilloma virus, Influenca virus, *Salmonella, neisseria, Borrelia, Chlamydia, Bordetella, Plasmodium* and *Toxoplasma*.

14. A pharmaceutical composition useful for adjuvanting an immune response comprising an adjuvanting effective combination of QS21 and 3-De-O-acylated monophosphoryl lipid A (3D-MPL).

15. The composition as claimed in claim 14 capable of invoking a cytolytic T cell response in a mammal to an antigen or antigenic composition.

16. The composition as claimed in claim 14 capable of stimulating interferon γ production.

17. A method for stimulating a cytotoxic T cell response in an animal comprising introducing into said animal a cytotoxic T cell response stimulating amount of the composition of claim 1.

18. A method for stimulating a γ-interferon response in an animal comprising introducing into said animal a γ-interferon response stimulating amount of the composition of claim 1.